

Angiographic and risk factor characteristics of subjects with early onset ischaemic heart disease

S NITTER-HAUGE, J ERIKSEN, E THAULOW, K VATNE

From the Laboratory of Cardiology, Medical Department B, and Department of Radiology, Rikshospitalet, The National Hospital, University of Oslo, Oslo, Norway

SUMMARY Sixty-six consecutive patients less than 40 years of age with angiographically documented coronary artery disease and coronary heart disease took part in a study aimed at (1) identifying the presence of factors which might explain the premature onset of ischaemic heart disease, and (2) assessing the distribution and severity of the coronary artery lesions.

For comparisons we have used a study of risk factors in 1832 men defined as "normals" according to a recent comprehensive examination.

The findings show that the typical early onset coronary heart disease case is an overweight, heavily smoking male "blue collar" worker, with high serum levels, a marginally raised blood pressure, and a high prevalence of coronary heart disease among first degree relatives.

Coronary angiography showed a preponderance of one vessel disease. In particular, left anterior descending artery lesions were common, which might have contributed to the early manifestation of disease.

Even in countries where coronary artery disease and coronary heart disease are most prevalent coronary heart disease is a disease occurring mostly in men over 40 years of age and in women over 50 years of age. Epidemiological studies have convincingly shown that coronary artery disease and coronary heart disease are not inevitable consequences of ageing, but represent a disorder more or less strongly related to the presence of a host of biochemical aberrations, genetical factors, personal habits, and environmental factors.¹ There exists a vast body of published reports on the relation between coronary artery disease/coronary heart disease and such factors, labelled as coronary risk factors.^{2,3}

Since coronary heart disease in the young is a rare disease, little is known on whether it has distinct patterns or only closely mimics coronary heart disease in the old or middle-aged person.

The present report deals with all patients less than 40 years of age with an angiographically proven diagnosis of coronary heart disease made in our department in the years 1972 to 1978. The specific aims of the present study were:

- (1) To assess if there exists particular clinical, socio-economic, or coronary risk factor patterns among young coronary heart disease subjects.

- (2) To evaluate the extent and severity of the atheromatous lesions in young coronary heart disease subjects.

Subjects and methods

We studied 66 subjects (59 men and seven women), nine below 30 years (all men) and 57 between 30 and 39 years. They represented all cases with a diagnosis of coronary heart disease admitted in our department in the years 1972-1978. Forty-two (64%) had scalar electrocardiographic signs of myocardial infarction, and all had had their infarction more than six months before the examination in our hospital. The remaining 24 (36%) had angina pectoris only. Using the NYHA classification, nine (14%) had angina of grade 4, 14 (21%) were in grade 3, 35 (53%) in grade 2, and eight (12%) in grade 1. The duration of angina was 22.4 months on average (range one to 90 months). Men and women were grouped together since there was no indication of any sex differences in the variables studied.

RISK FACTORS

A subject was considered to have *hypertension* if he (or she) was treated for hypertension on admission, or if the lowest recorded diastolic blood pressure during the stay in our department was ≥ 100 mmHg, measured with a mercury sphygmomanometer.

Hypercholesterolaemia was defined as a fasting serum level of cholesterol ≥ 8.8 mmol/l, that is values above the 97.5 centile for apparently healthy men aged 40 to 44 years.⁴

Hypertriglyceridaemia was defined as fasting values exceeding 3.0 mmol/l, that is values in excess of the 97.5 centile as mentioned above.⁴

Smoking was defined as regular smoking of \geq five cigarettes a day (only two of the 66 subjects smoked one to four cigarettes a day).

Family coronary heart disease was defined as coronary heart disease (angina and/or myocardial infarction) diagnosed in grandparents, parents, or sibs below the age of 50 years.

Overweight was defined as a body weight $\leq 20\%$ above standard weight.⁵

Type of work or *occupation* was crudely divided into "white"- and "blue collar" work.

For comparisons we have used a study of risk factors in 1832 men defined as "normals" according to a recent comprehensive examination.⁴⁻⁸ This group is a subsample from a group of 2014 apparently healthy men aged 40 to 59 years from five companies or governmental agencies in Oslo, Norway, who recently participated in a cardiovascular survey examination in our department. The survey examination included: full clinical examination, resting electrocardiogram, a near maximal bicycle exercise electrocardiogram test, a panel of blood tests, and coronary angiography in subjects with a strong suspicion of latent coronary heart disease according to our survey criteria. Blood pressure represents the mean of three consecutive measurements on the same day. A subject was considered to have hypertension if the diastolic blood pressure was ≥ 100 mmHg, measured with a mercury sphygmomanometer. The details about selection and examination procedures are reported elsewhere.⁴⁻⁸ In particular, it should be emphasised that all men with known or suspected heart disease were excluded before the survey. From the 2014 participating men, 115 fulfilled our criteria for coronary angiography to be performed⁶⁻⁷; 35 had chronic chest pain, probably of non-coronary origin, and 32 had slight, albeit typical angina pectoris not fulfilling our angiography criteria.⁶⁻⁷ These 182 men were excluded from the present report leaving 1832 as a "normal" reference group. Since blood pressure and cholesterol increase with age, statistically "normal" values for younger subjects would be lower.

Hence a comparison of data from our 1832 "normals" with data from our young patients with coronary heart disease to some extent underestimates the aberrations from "normal" among the latter.

ANGIOGRAPHY

All subjects underwent a complete angiographic study

of the left ventricle and coronary vessels. Left ventricular angiograms were obtained in the right anterior oblique position with additional projections if there was suspicion of left ventricular aneurysms. Selective coronary angiography was performed with the technique of Judkins.⁹ In all subjects coronary angiograms were taken from the left and right anterior oblique position, left lateral and left hemiaxial projection (main stem projection). Additional projections were taken when necessary to have free projections of the vessels.

The extent of atheromatosis according to the angiograms was classified as:

- (A)
 - (i) Normal vessel, that is no obstruction or irregularity seen.
 - (ii) Insignificant coronary artery disease (1 to 49% luminal obstruction).
 - (iii) Significant coronary artery disease, haemodynamically insignificant (50 to 74% obstruction).
 - (iv) Significant coronary artery disease, haemodynamically significant ($\geq 75\%$ obstruction). In Fig. 3 (p. 328) group 4 has been further subdivided in cases with 75 to 89%, 90 to 99% obstruction, and complete occlusions.

The angiograms were read and reread as reported previously.⁶ The four major coronary arteries and their main secondary branches were considered separately, that is, left main coronary artery, left anterior descending, circumflex artery, and right coronary artery, and the main secondary branches such as diagonal and obtuse branch, and right posterior descending branch of a dominant right coronary artery.

(B)

In the following, one, two, and three vessel disease refer to obstructions $\geq 75\%$ of one, two or three vessels, with left main stem stenosis $\geq 75\%$ counting as an obstruction of two vessels.

Ejection fraction was determined with conventional technique by measuring the difference between end-diastolic and end-systolic area on the cineangiogram. In the presence of aneurysms two projections at right angles to each other were used for the measurement.

Results

RISK FACTORS

Hypertension was present in 16/66 (24%), which is more than double the prevalence of hypertension in our group of 1832 healthy men 40 to 59 years of age (8%) ($p < 0.01$).

Hypercholesterolaemia was present in 23/66 (35%)

and hypertriglyceridaemia in 27/66 (41%). Hypercholesterolaemia and/or hypertriglyceridaemia was present in 38/66 (58%). Mean serum cholesterol and triglyceride values were 8.2 mmol/l and 2.4 mmol/l, respectively. Fig. 1 and 2 show the distribution of serum cholesterol and triglycerides compared with the values found in 1832 apparently healthy men aged 40 to 59 years.⁴ It is seen that there is a considerable shift of values to the right among the coronary heart disease subjects ($p < 0.001$ for both triglycerides and cholesterol).

Smoking Of 66, 57 were currently smoking (86%) vs. 45% among the 1832 healthy subjects ($p < 0.001$). Only four had never smoked.

Overweight was present in 30% as compared with 12% among the 1832 apparently healthy men

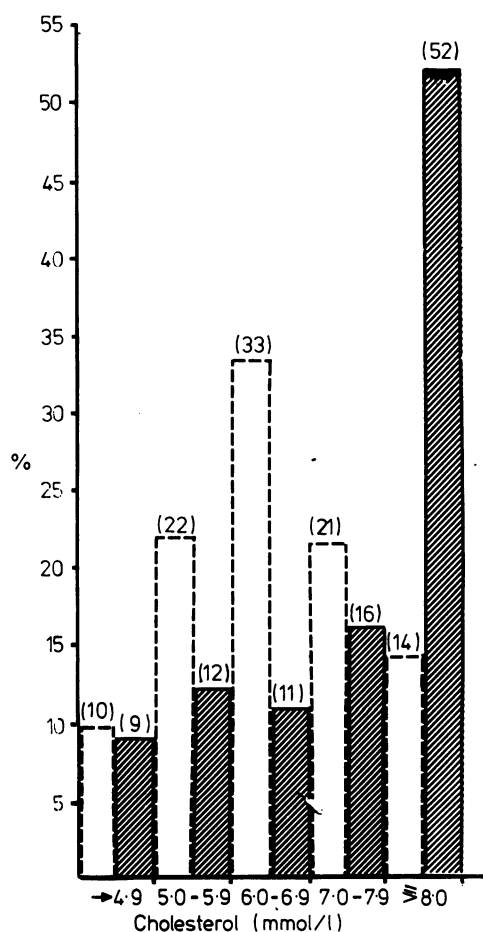


Fig. 1 Distribution of serum cholesterol in 66 patients with early onset ischaemic heart disease (hatched columns) and in 1832 normals (open columns).⁴

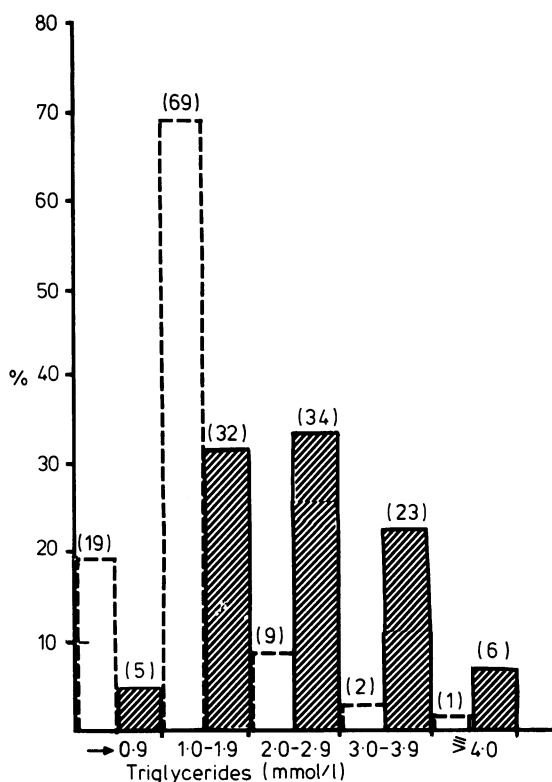


Fig. 2 Distribution of serum triglycerides in 66 patients with early onset ischaemic heart disease compared with normals.⁴ Symbols as in Fig. 1.

($p < 0.01$). Overweight was highly significantly associated with hypertriglyceridaemia and hypertension.

Family coronary heart disease was present in 29/66 (44%), but only in 5% among the apparently healthy men ($p < 0.001$).

Myocardial infarction was present in 42/66 (64%).

Occupation: 45 (68%) (39 men and six women) were manual workers, mostly heavy physical work. The distribution of this variable was unknown among the control subjects, but the proportion of manual workers far exceeded what would be expected on a community base.

Disregarding overweight the following risk factor distribution was found among the young subjects with coronary heart disease:

One risk factor 15/66 (23%), two 21/66 (32%), three 15/66 (23%), four 10/66 (15%), and five in 3/66 (4.5%). Only two (3%) did not have any coronary risk factor present, whereas 28/66 (42%) had \geq three risk factors.

ANGIOGRAPHIC FINDINGS

Severity of coronary artery disease

The changes found in the left main coronary artery and in each of the three major coronary arteries are shown in Fig. 3. It is seen that there was significant haemodynamic stenosis in left main coronary artery in 8%, in the left anterior descending artery in 76%, in the circumflex artery in 44%, and in the right coronary artery in 50%.

Distribution of coronary artery disease

This series of patients has also been reviewed concerning the presence of one, two, or three vessel disease. Thirty-one patients (47%) had significant one vessel disease, 19 (29%) had two vessel disease, and 16 patients (24%) three vessel disease (Fig. 4).

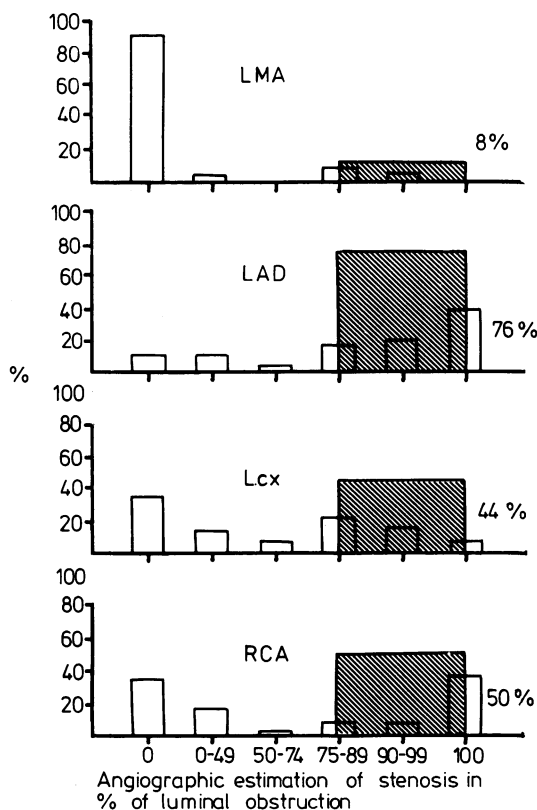


Fig. 3 Distribution of coronary artery stenosis expressed in percent of luminal obstruction in 66 patients with early onset ischaemic heart disease. LMA, left main coronary artery; LAD, left anterior descending artery; Lcx, left circumflex artery; RCA, right coronary artery. Hatched area marks the total percentage of arteries with significant stenosis $\geq 75\%$.

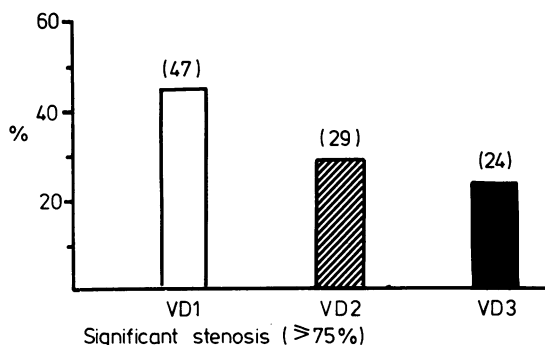


Fig. 4 Distribution of single vessel disease (VD1), double vessel disease (VD2), and triple vessel disease (VD3) in 66 patients with early onset ischaemic heart disease.

Mitral regurgitation was found in five of 66 (7%).

Localised aneurysms were present in only nine of 66 (14%) whereas regional dyskinesia was seen in 31 of 66 (47%) among the young subjects studied.

Ejection fraction was 61%. Twelve had an ejection fraction less than 50%, seven from 50 to 59%, and the remaining $\geq 60\%$.

Discussion

The application of coronary angiography and left ventricular angiography adds new dimensions to the study of the extent and severity of coronary heart disease, as well as the association between coronary heart disease and the so-called coronary risk factors. Thus, it has been shown convincingly that several patients with a diagnosis of coronary heart disease made on clinical grounds have completely normal coronary arteries,¹⁰⁻¹² in particular in subjects below 40 years with a diagnosis of angina pectoris. In a previous study from our department 25% of the men and more than 50% of the women in this age group proved to have normal coronary arteries on the angiograms.¹³ Inclusion of such cases in a study on the association between coronary heart disease and risk factors might severely dilute findings in true coronary artery disease. Mean values of cholesterol, triglycerides, and cigarettes smoked would have dropped considerably if we had reported data from all patients less than 40 years referred with a preangiographic diagnosis of coronary heart disease (that is based on clinical criteria only).¹³

The present series of young patients with documented coronary heart disease differs from most other studies of early onset ischaemic heart disease because we have included only those with angiographically proven coronary artery disease.¹⁴⁻²¹ All had developed their clinical symptoms of disease and were

admitted in our department before 40 years of age. Some bias may have operated by preferential reference of patients with an unrepresentatively high prevalence of risk factors. In spite of this, we feel that the material can be used to elucidate aspects of premature onset ischaemic heart disease.

From our study, it seems justified to conclude that the typical patient with early onset coronary heart disease is an overweight man who smokes heavily and has a marginally raised blood pressure and high serum lipids. There is also a high prevalence of coronary heart disease among first degree relatives, and the patient is a "blue collar" worker.

The present material in all respects seems to corroborate and amplify previous reports and concepts on the association between coronary heart disease and various coronary heart disease risk factors.^{2 3 14 15 17 19 20}

Despite our very wide ranges for "accepted normal values" on the variables studied only two of the 66 had normal values for all variables selected. In addition, one of these two was a young woman who had suffered an extensive anterior myocardial infarction. She had taken oral contraceptives for four to five years before her myocardial infarction. Angiographically she had an anterior aneurysm, centrally occluded left anterior descending artery, but otherwise normal coronary arteries. The association between premenopausal coronary heart disease and the use of oral contraceptives has been reported in detail previously.²² Thus, in our experience coronary artery disease only very rarely presents as coronary heart disease unless at least one severe aberration of well accepted coronary heart disease risk factors is present. In fact, the majority (75%) in our material had pathological values of at least two risk factors, and 42% had three or more risk factors present.

The independent contribution to coronary heart disease of each risk factor is difficult to assess in a study such as this. It seems, however, as if smoking plays an important role, at least in combination with severe hyperlipidaemia.^{8 14 17 19} Of the lipid aberrations, hypercholesterolaemia seems far more important than hypertriglyceridaemia. The combined data also indicate that early onset coronary heart disease almost never occurs unless specific, significant aberrations of one or more well-known risk factors are present.

It is also noteworthy from the composition of our material that the majority of our cases were "blue collar" workers. This to some extent corroborates the recent notion that coronary heart disease in our part of the world is a disease which strikes more people of the lower social classes.²³⁻²⁵ Another explanation might be that "blue collar" workers with strenuous physical work might more easily develop symptoms from

progressive coronary artery disease. Hence it is conceivable that coronary artery disease develops as early in "white"- as in "blue collar" workers, but that symptoms are recognised earlier in "blue collar" workers with a high physical demand at work. Recent epidemiological studies, however, indicate a more direct association between coronary heart disease and the lower social classes.²³⁻²⁵

Since coronary atherosclerosis is a gradual and progressive disease, one might expect less extensive atheromatosis in our young group than in older patients. This is also the experience in our department. In contrast, our young patients showed a preponderance of one vessel disease. In a recent consecutive series from our department, of 636 subjects with coronary heart disease who were over 40 years of age, 31% of whom had had one or more myocardial infarctions, only 13% had one vessel disease, 30% had two vessel disease, and as many as 57% had three vessel disease. In this older coronary heart disease group there was also a strikingly similar distribution of one, two, and three vessel disease in all decades above 40 years of age.¹³ Thus, as mentioned above, 47% of the young subjects had one vessel disease, 29% had two vessel disease, and only 24% had three vessel disease. This difference in extent of coronary artery lesions among subjects below and above 40 years of age is highly significant ($p < 0.01$).

It might be argued that a difference in duration of symptoms between younger and older patients might explain this difference in extent of disease. Younger subjects might conceivably be referred far earlier than older subjects. A mean duration of the case history only 12 months less among the young subjects, however, can hardly explain these major differences in angiographic patterns.

Thus, our young patients had less extensive coronary artery disease but more frequent myocardial infarctions than patients over 40 years of age. It is also seen that according to the ejection fraction values very few had signs of severe left ventricular impairment.

The preponderance of left anterior descending artery lesions in subjects with coronary heart disease is the same among our patients as in other angiographic studies, including one study in patients with few or no symptoms.^{6 26 27} It has also been suggested that ischaemia of the posterior and inferior wall may be more difficult to detect on the exercise electrocardiogram²⁶ and it is conceivable that symptoms and/or electrocardiographic signs arising from these parts of the myocardium may more often give rise to misinterpretation, with a delay in making a diagnosis and referring the patients.

Although no hard evidence is present we have the impression that collaterals were less developed among the young than the older subjects. Conceivably the

course of coronary artery disease had been particularly malignant among the young patients, rendering too little time for collaterals to be developed, since collaterals occur in response to longstanding, chronic ischaemia. This concept is in line with the acute onset of coronary disease symptoms in most of our cases in the early onset coronary heart disease group, and is also supported by the fact that the majority of our subjects had hard manual work. Thus, if anything, one should rather have expected more collaterals in physically active than in more inactive subjects.

Recent studies indicate a severe prognosis in early onset coronary heart disease.^{28 29} Since angiography may indicate less advanced coronary artery disease, at the onset of symptoms the poor long-term prognosis is unexpected. This suggests that coronary heart disease often runs a malignant, progressive course in the years after the first clinical event. Such individuals therefore deserve close supervision and intensive preventive treatment.

References

- 1 Peacock PB. Atherosclerotic heart disease and the environment. *Ann NY Acad Sci* 1973; **35**: 631-5.
- 2 Simborg DW. The status of risk factors and coronary heart disease. *J Chronic Dis* 1970; **22**: 515-52.
- 3 Epstein FH, Ostrander LD. Detection of individual susceptibility toward coronary disease. *Prog Cardiovasc Dis* 1971; **13**: 324-42.
- 4 Erikssen J, Skrede S. Serum lipids and latent coronary insufficiency. *Scand J Clin Lab Invest* 1977; **37**: 243-50.
- 5 Metropolitan Life Insurance Company. Rise in mortality last year. *Stat Bull Metropol Life Ins Co* 1959; **40**: 1-7.
- 6 Erikssen J, Enge I, Forfang K, Storstein O. False positive diagnostic tests and coronary angiographic findings in 105 presumably healthy males. *Circulation* 1976; **54**: 371-6.
- 7 Erikssen J, Rasmussen K, Forfang K, Storstein O. Exercise ECG and case history in the diagnosis of latent coronary heart disease among presumably healthy middle-aged men. *Eur J Cardiol* 1977; **5**: 463-76.
- 8 Erikssen J, Enger SC. Smoking, lung function, physical performance and latent coronary heart disease in presumably healthy middle-aged men. *Acta Med Scand* 1978; **203**: 509-16.
- 9 Judkins MP. Percutaneous transfemoral selective coronary arteriography. *Radiol Clin North Am* 1968; **6**: 467-92.
- 10 Friesinger GC, Smith RF. Correlation of electrocardiographic studies and arteriographic findings with angina pectoris. *Circulation* 1972; **46**: 1173-84.
- 11 Campeau L, Bourassa MG, Bois MA, et al. Clinical significance of selective coronary cinearteriography. *Can Med Assoc J* 1968; **99**: 1063-8.
- 12 Proudfit WL, Shirey EK, Sones FM, Jr. Selective cine coronary arteriography. Correlation with clinical findings in 1000 patients. *Circulation* 1966; **33**: 901-10.
- 13 Storstein O, Enge I, Erikssen J, Thaulow E. Natural history of coronary artery disease studied by coronary arteriography, a 7 year study of 795 patients. *Acta Med Scand* 1981; In press.
- 14 Dolder MA, Oliver MF. Myocardial infarction in young men. Study of risk factors in nine countries. *Br Heart J* 1975; **37**: 493-503.
- 15 Rissanen AM, Nikkilä EA. Coronary artery disease and its risk factors in families of young men with angina pectoris and in controls. *Br Heart J* 1977; **39**: 875-83.
- 16 Goldstein JL, Schrott HG, Hazzard WR, Bierman EL, Motulsky AG. Hyperlipidemia in coronary heart disease II. Genetic analysis of lipid levels in 176 families and delineation of a new inherited disorder, combined hyperlipidemia. *J Clin Invest* 1973; **52**: 1544-68.
- 17 Nikkilä EA, Aro A. Family study of serum lipids and lipoproteins in coronary heart disease. *Lancet* 1973; **i**: 954-9.
- 18 Gertler MM, White PD. *Coronary heart disease in young adults; a multidisciplinary study*. Cambridge, Massachusetts: Harvard University Press, 1954.
- 19 Oliver MF. Ischaemic heart disease in young women. *Br Med J* 1974; **iv**: 253-259.
- 20 Hatch FT, Reissell PK, Poon-King TMW, Canellos GP, Lees RS, Hagopian LM. A study of coronary heart disease in young men. Characteristics and metabolic studies of the patients and comparison with age-matched healthy men. *Circulation* 1966; **33**: 679-703.
- 21 Bergstrand R, Vedin A, Wilhelmsson C, Wallin J, Wedel H, Wilhelmsen L. Myocardial infarction among men below age 40. *Br Heart J* 1978; **40**: 783-8.
- 22 Radford DJ, Oliver MF. Oral contraceptives and myocardial infarction. *Br Med J* 1973; **iii**: 428-30.
- 23 Antonovsky A. Social class and the major cardiovascular diseases. *J. Chronic Dis* 1968; **21**: 65-106.
- 24 Shekelle RB, Ostfeld AM, Paul O. Social status and incidence of coronary heart disease. *J. Chronic Dis* 1969; **22**: 381-94.
- 25 Holme I, Helgeland A, Hjermann I, Lund-Larsen PG, Leren P. Coronary risk factors and socioeconomic status. The Oslo study. *Lancet* 1976; **ii**: 1396-8.
- 26 McHenry PL, Phillips JF, Knoebel SB. Correlation of computer-quantitated treadmill exercise electrocardiogram with arteriographic location of coronary artery disease. *Am J. Cardiol* 1972; **30**: 747-52.
- 27 Abrams HL, Adams DF. The coronary arteriogram (second of two parts). Structural and functional aspects. *N Engl J Med* 1969; **281**: 1336-42.
- 28 Piessens J, Vanhaecke J, Willems JL, DeGeest H. Coronary arterial lesions in young men who survived a transmural myocardial infarction. Abstract no 1179, VIII European Congress of Cardiology, Paris, June 1980.
- 29 Shapiro LM, Howat AP, Singh SP. The prognosis of young survivors of myocardial infarction. Abstract no 2667, VIII European Congress of Cardiology, Paris, June 1980.

Requests for reprints to Dr S Nitter-Hauge, Department of Cardiology, Medical Department B, Rikshospitalet (University Hospital), Oslo 1, Norway.